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Review Article

Unveiling the relevance of the redox character of nitroaromatic and nitroheteroaromatic compounds as potential medicines

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Abstract

This review discusses the state of the art, challenges, and perspectives in recent applications of nitroaromatics and nitroheteroaromatics, which are redox-bio-activated drugs or leads, in Medicinal Chemistry. It deals mainly with the electrochemical approach toward the electron transfer-based molecular mechanisms of drug action, drug design, estimation and measurement of redox potentials, correlation of physicochemical and pharmacological data, and electrochemical studies of the main representatives of nitro-containing prodrugs, along with approaches to combat their toxicity issues, aiming at a better therapeutic profile. Electrochemical investigation plays essential roles, being strategic in the design and discovery of potential medicines.

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Introduction

Life depends on molecular interactions, in particular, redox reactions. As such, electrochemical methods have become a powerful complementary tool for the characterization and design of redox-modulating agents [1–3], for example, in drug metabolism and toxicological studies where mimics have been used to understand phase 1 metabolic processes involving CYP450-mediated oxidation and enzymatic bio-reductions [4–6]. Such *in vitro* studies lead to an understanding of *in vivo* metabolism, crucial for drug discovery, clinical pharmacology, toxicology, and therapeutics [7,8]. A recent example of the power of electrochemistry in this area is the coupling of electrochemistry-based mass spectrometry (MS) [4–6,9] with electrosynthesis [10] to answer many questions about the metabolic behavior of several compounds [4–7,9,10]. Another common approach is studying therapeutically inactive prodrugs that can be deliberately activated through redox-biotransformation to the active form [2,3,7] and subsequently interrogated. Electrochemical systems using biomimetics and/or prodrugs for drug development are attractive due to their low cost, the ease of application, the use of a mass-free reagent (the electron), and they do not present any ethical issues regarding the use of living subjects or animal tissues.

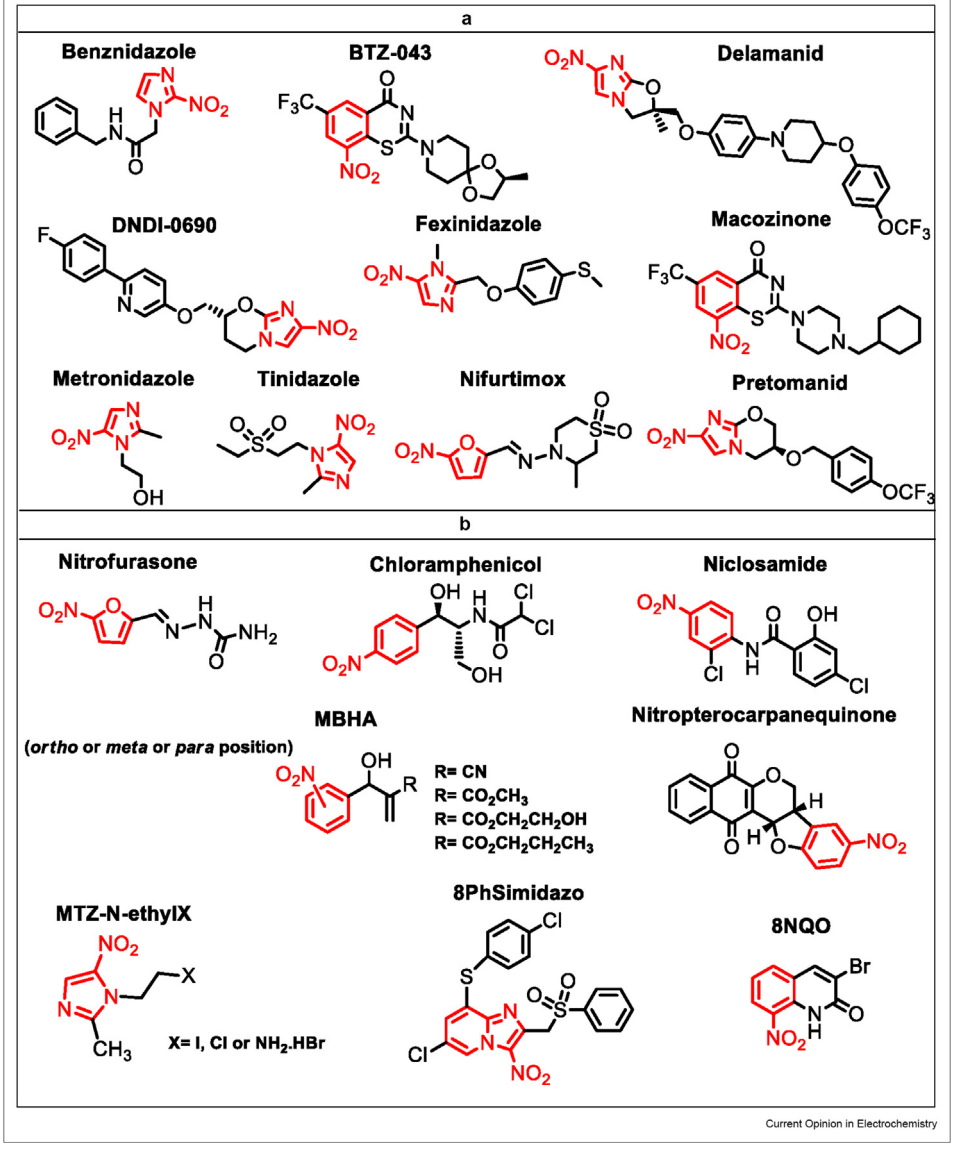
A significant class of electroactive organic compounds, essentially prodrugs, are nitroaromatics [11–14]. The nitro group plays fundamental roles in several scientific fields since the more recent in organic electronics [15], in environmental chemistry, and mainly in medicinal chemistry, where it has always been considered to have a double-sword nature, with prolonged use in therapeutics, however, still considered a toxicophore [11–14]. Nitroaromatics are associated with mutagenicity, carcinogenicity, hepatotoxicity, and genotoxicity [11–14]. Due to a better understanding and new technological advances, it is possible to overcome noxious effects favoring the beneficial ones [16].

Figure 1a/b display the structures of the most clinically important nitro-compounds where those under the A heading are considered 'essential' (appear in 'Drugbank' and/or the WHO's list of essential drugs), whereas those under the B heading are deemed 'relevant' nitro-compounds with reported biological activity and electrochemical data.

The repositioning of existing drugs or drug-like molecules with known pharmacokinetics and safety profiles has been an alternative strategy for a rapid approach to identifying new effective and safe drugs. Thus, current nitro-based antiparasitic drugs are not only viable for the treatment of helminth and protozoan infections (Figure 1a) but are also important candidates for new pharmacological treatments [17], including for cancer [18,19].

Because of its ability to easily undergo reduction at the molecular level where follow-up bond−cleavage reactions can generate localized, highly reactive, electrophilic sites [12,20,21] the nitro-group is considered versatile and essential for biological activity. As such, investigating the fundamental molecular-level electrochemical behavior of nitroaromatic and heteroaromatic compounds [22] is important for understanding their biological and medicinal activities. Electrochemical studies of nitro-compounds date back to the early 1900s

Figure 1



Structures of the most clinically relevant nitrocompounds **(a)**: Nitrocompounds classified as essential drugs; **(b)**: other nitroderivatives with relevant biological activities and studied by electrochemical methods. The authors gave some of the acronyms.

[22] and are continuously and comprehensively reviewed in excellent books and articles [2,23–25].

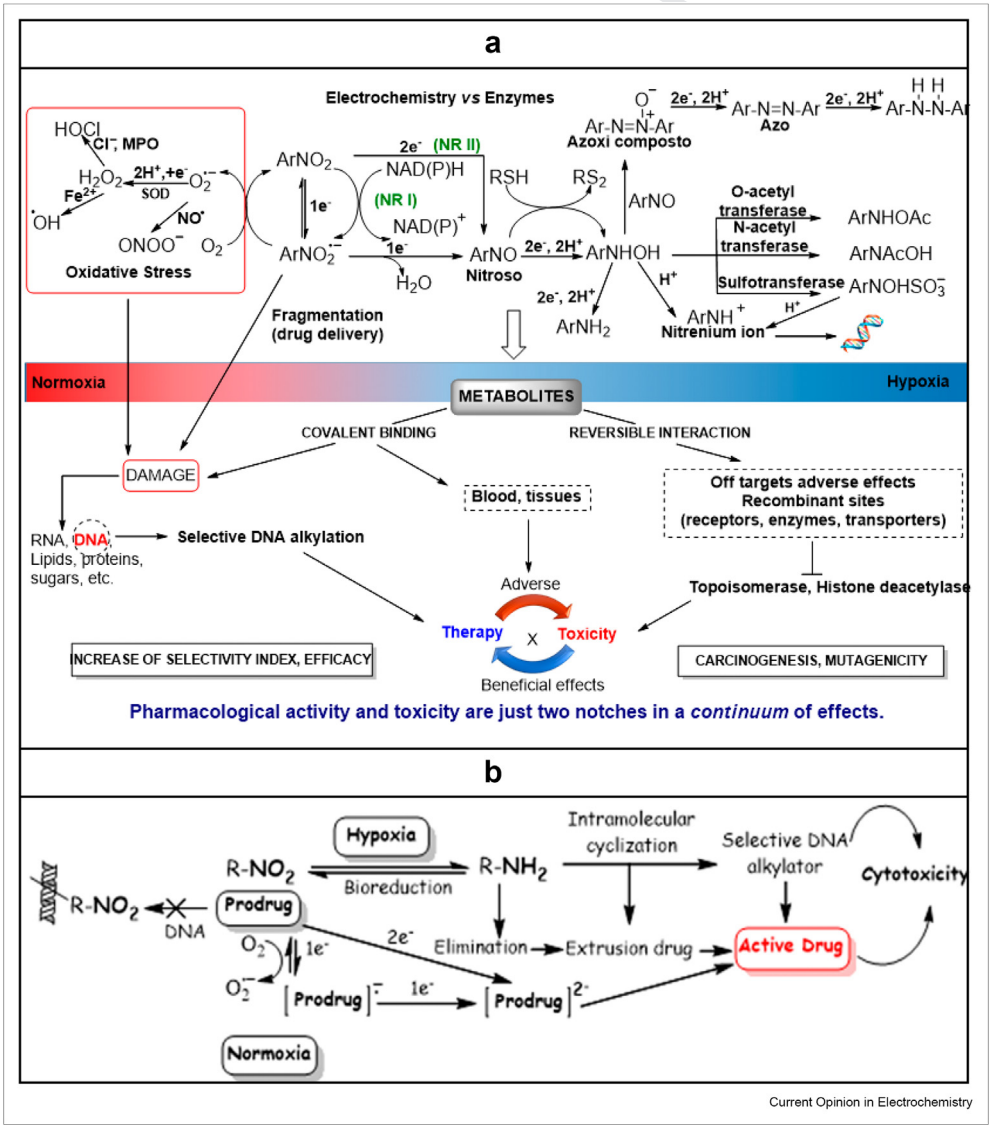
Nitrocompounds: relevance and molecular mechanisms of action

The modes of action of nitrofurans, nitroimidazoles and other nitrocompounds are not fully understood, but the common pathways are represented in Figure 2.

It is broadly recognized that biological activities correlate with the redox properties of the nitro group and the stability or the reactivity of generated reduced compounds, which can react with biological nucleophilic targets such as proteins, nucleic acids, aminoacids, and enzymes, to induce desired or undesired biological changes [11,12,14,16,21] (Figure 2a, b).

The biological activity also depends on the medium's oxygen content where it plays its role (normoxia: red color versus hypoxia: blue color, Figure 2). Hypoxia is a state of low oxygen tension found in numerous solid tumors or other conditions. It is typically associated with abnormal vasculature, which results in a reduced supply of oxygen and nutrients and impaired delivery of drugs [11,12]. The molecular oxygen level of normal tissues is 2%–9% v/v (on average 40 mm Hg pO_2) [12]. In contrast, in the hypoxic microenvironment, the O_2 level can reach 0.02%–2% v/v (below 10 mm Hg pO_2) [12].

Figure 2



(a) A closer look at the molecular mechanisms of action of nitroaromatics. Adapted from Refs. [7,11,12,20]. **(b)** A general scheme related to the alkylation of DNA through reductive elimination. Adapted from Ref. [20].

Legend: NRI: type I nitroreductase, NRII: type II nitroreductase, NAD(P)H: nicotinamide adenine dinucleotide (phosphate) reduced, $NAD(P)^+$: nicotinamide adenine dinucleotide (phosphate) oxidized, MPO: myeloperoxidase, SOD: superoxide dismutase, RSH: thiols, RS_2: disulfide, RNA: Ribonucleic acid.

The process of electron transfer is essential. Electrochemical studies of $ArNO_2$, in protic, aprotic, mixed, micellar, membrane-mimicking media, surface modifiers, surfactants, with several electrodes [22] can contribute to the understanding of their biological activities [1,5,6,9,10,12,21,23,24].

The redox process, in the laboratory, can be compared to the *in vivo* enzymatic one, allowing the first reduction step by the capture of one electron, leading to $ArNO_2^{\bullet-}$, typically obtained in aprotic, mixed or more basic protic media, or by multiple electronic steps leading to the different intermediates, practically to nitroso (ArNO), hydroxylamine (ArNHOH), amine ($ArNH_2$), azo (ArN=NR), azoxy (ArNO=NAr), nitrenium ($ArNH^+$), hydrazines (ArNH-NHAr) and others (Figure 2a).

The enzymes catalyze *in vivo* redox reactions. The nitroreductases (NTR) are a family of FMN- or FAD-dependent enzymes capable of metabolizing nitroaromatic compounds. NTRs utilize NADH or NADPH as reductive cofactors [11,14,20]. The NTRs are subdivided into two reduction types, depending upon their reaction mechanisms. Type I NTRs catalyzes, under anaerobic conditions, the reduction of $ArNO_2$ to produce biologically active reduced derivatives, including nitrenium ions, which have a higher protein binding affinity, compared to type II intermediates. Under aerobic conditions, nitroreduction catalyzed by type II NTRs produces reactive oxygen and nitrogen species (ROS/RNS), causing oxidative stress to pathogens and their ultimate death (Figure 2a) [20]. However, it also causes deleterious mutagenicity and toxicity [11,13,20].

Selective DNA alkylation (Figure 2a and b) is one of the most important molecular mechanisms. Electrochemical methods are advantageous in this topic, as they allow the *in situ* and real-time redox activation of pro-drugs [26–30].

Nitrocompounds: electrochemistry

The determination of the standard potential ($E^{\circ'}$, E_{redox}, $E_{1/2}$, $Ep_{1/2}$), experimentally or by computational ways, together with an estimation of kinetic data, results from several electrochemical techniques, *in situ* experiments, electrochemically based hyphenated ones, and others, and provide essential data to evaluate some of the main physicochemical properties and the chemical outcomes of the analyzed compounds. In many cases, these electrochemical parameters play a critical but rarely a decisive role [1,2,31].

The majority of electrochemical and computational studies have been used to obtain and estimate the E_{redox} values ($ArNO_2/ArNO_2^{\bullet-}$), for the generation of a persistent radical anion, through a reversible single electron transfer, at the first wave potential, in an aprotic medium. Some specialty solvents, like liquid and supercritical ammonia and room temperature ionic liquids, were also used to mimic the nonpolar environment in the cell, for instance, at the cell membranes [1–3,28], and the catalytic sites of some enzymes. Nonacidic conditions, in order to avoid protonation of the radical anions, in aqueous solutions or mixtures with an organic solvent, have also been used [22,27,28,32–34]. Structural aspects are also important to the stability of the radical anion nitro: the presence of acidic hydrogen (may cause self-protonation or interactions through hydrogen bonding) [34], of a high local spin density (causing a coupled chemical reaction), the existence of potential leaving groups (leading to reductive elimination) [35–37] or the possibility of ring fragmentation [14], among others, may lead to unstable electrogenerated intermediates.

The experimental values of $E^{\circ\prime}$ have been found to correlate linearly with calculated values of E_{LUMO} [38]. Several advances in computer technology/DFT level of theory and reduction data for nitroaromatics can be obtained [39]. Pulse radiolysis had also been used but is out of the present review's scope, despite its relevance [40,41].

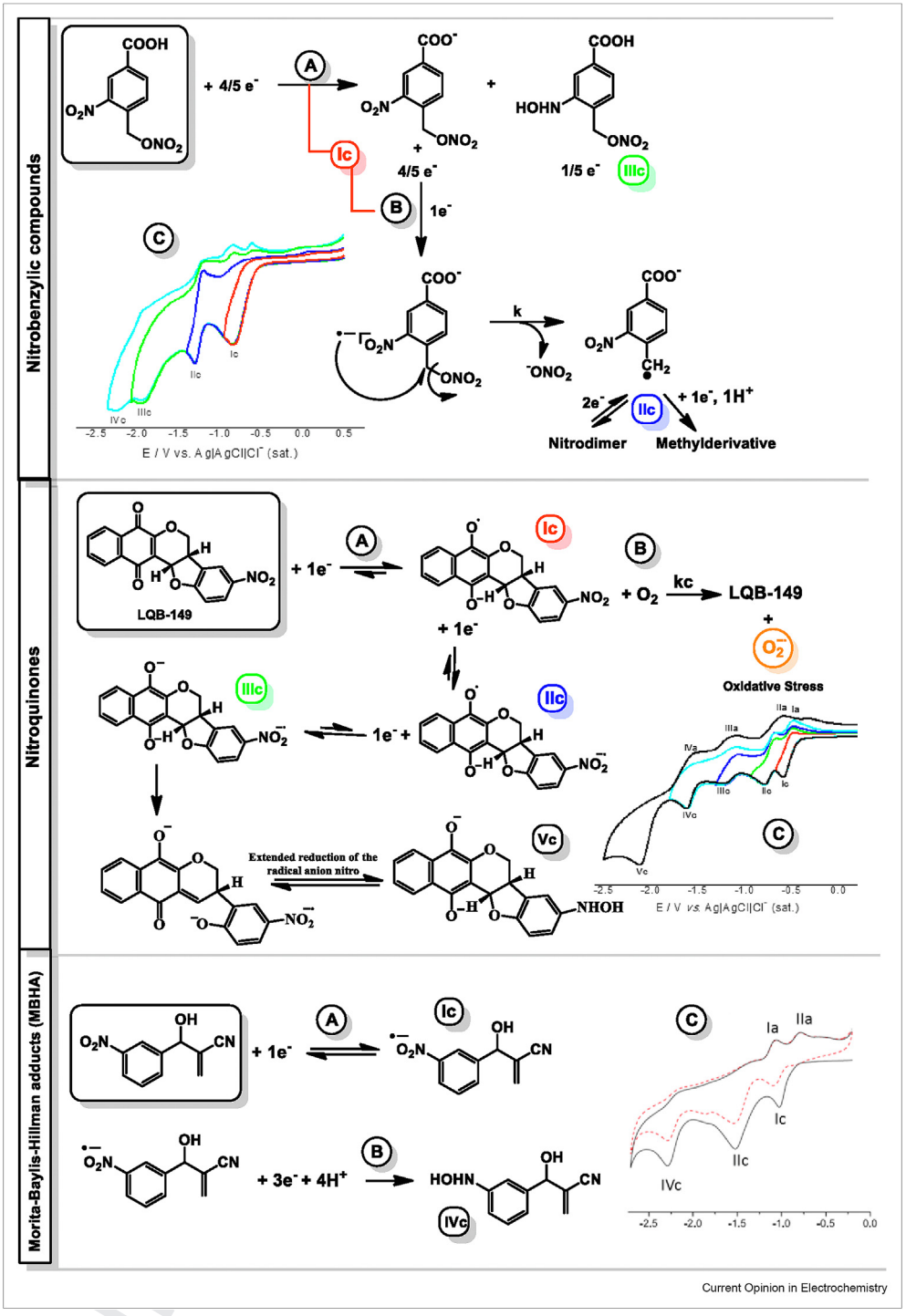
Figure 3 displays several electrochemical results, with the presentation of cyclic voltammograms, which allow the understanding of the electronic mechanisms and point to the potential use of electrochemistry toward the rationale/practice of medicinal chemistry.

The following classes of electroactive nitro-containing drugs are some of the most promising leads in medicinal chemistry.

Nitroimidazoles

Nitroimidazoles [42], represented, in Figure 1a, as benznidazole [43], metronidazole [44], tinidazole, pretomanid [45] (essential drugs), along with MTZ-N-ethylX and 8PhSimidazo are versatile aromatic heterocycles (Figure 1b), and often explored as a bioreductive and hypoxia-selective [14,41] (Figure 2) class of compounds [46–48]. Delamanid (Figure 1a), a drug for tuberculosis and Visceral Leishmaniosis (VL), and DNDi-0690, a delamanid–derived 2-nitroimidazooxazine, in phase-I clinical trials against VL, illustrate well the strong potential of nitroimidazoles in the search for novel drugs [14,46–48] (Figure 1). As

Figure 3

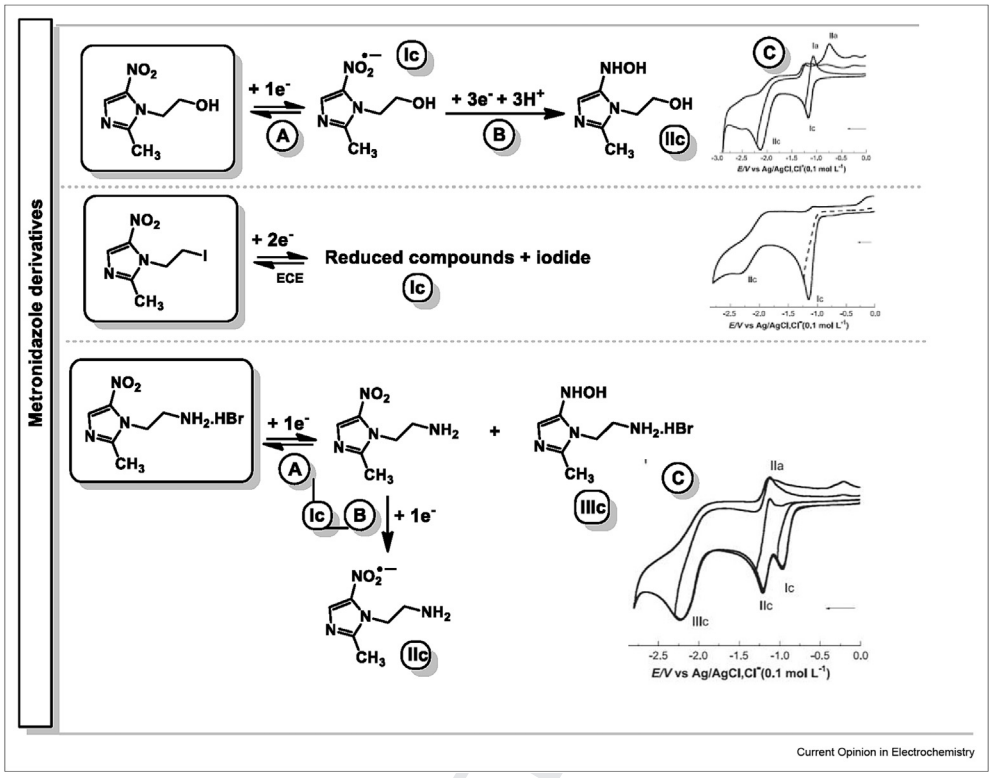


Cyclic voltammograms (CV) and schemes corresponding to the electrodic mechanisms, held in aprotic media, on glassy carbon electrode, for chosen nitroaromatics, classified as nitrobenzylic, nitroquinones, Morita-Baylis–Hillman adducts (MBHA), and metronidazole derivatives.

leishmanicidal, 8PhSimidazo (Figure 1) is the best hit, selectively bioactivated by the *Leshmania donovani* type 1 NTR1, with E_{redox} −0.63 V versus NHE, being neither mutagenic nor genotoxic, as well as its metabolites, thus, a right candidate for further *in vivo* studies [45].

Several metronidazole derivatives (MTZ-N1-ethylX) (Figure 1b) were analyzed by CV, and their electrodic mechanisms were obtained, with correlation with biological activity [36]. Three of these compounds, namely, the iodo, bromo, and ammonium salt derivatives,

Figure 3



(*continued*)

showed significant anti-*Helicobacter pylori* (strain resistant to MTZ) activity. In an aprotic medium, the N1-ethyl-halogenated compounds (-I, -Br) showed the process to be an ECE system, with halide release, after electrons' uptake. This behavior represents a case of dissociative electron transfer (DET) [37]. For the ammonium salt, a self-protonation mechanism [22,34] was also evident. Concerning biological activity, despite the impossibility of establishing a correlation, it has been observed that the more electrophilic compounds showed better anti-*H. pylori* activity [36].

Nitroquinolinones

The reduction potentials of several 8-nitroquinolin-2(1H)-ones (8NQO) (Figure 1b) were obtained [49,50]. The authors performed an electrochemistry-guided SAR study and correlated theoretical and experimental standard redox potentials with a good correlation. They modulated the redox potential through substituent modification in both rings. An intramolecular hydrogen bond between the lactam ring and the nitro group was shown to be necessary for the anodic shift of the redox potential, along with the presence of electron-withdrawing groups. Only substrates easily reduced ($E_{redox} > -0.6$ V versus Normal Hydrogen Electrode, NHE) were active toward L. infantum. This was a very successful example of medicinal electrochemistry, allowing a rational conception guided by electrochemical parameters [49,50]. The 6-bromo and 6-chloro-derivatives were shown to be potent, selective, not genotoxic, being bioactivated by NTR-I [49]. They appear to be good candidates as antitrypanosomal lead compounds. Pharmacomodulation and electrochemical-guided analysis revealed new leads [50].

Any interaction that stabilizes the nitro radical anion and dianion in solution relative to the precursor makes reduction easier, including solvation, ion-pairing, hydrogen-bonding [22], and introduction of electron-withdrawing groups [51]. Due to a good correlation between theoretical and experimental electrochemical data, the prediction of the redox potential was possible and directed the synthesis of more promising active compounds [51].

Nitrofurans/nitrothiophenes

Nifurtimox (NFX, Figure 1a) after reduction suffers cleavage, and the electrogenerated compounds may react with DNA [26]. DNA sensors are devices useful for this type of biological screening [28,29].

Nitrobenzylic compounds

Nitrobenzyl compounds can be metabolized *in vivo* generating reactive intermediates that can act as redox cyclers or DNA alkylating agents (Figure 2), responsible for their numerous biological activities, especially antiparasitic and antitumor. As examples, dissociative electron transfer (DET) with the release of nitrate (reduced *in vivo* to NO) [35] and self-protonation [36], evinced in electrochemical investigations (Figure 3), were assumed as relevant for comparison with the *in vitro* antinoceptive and anti-inflammatory data [35].

Nitroquinones

Nitropterocarpanequinone (Figure 1b) [52], a parasiticidal agent, was thoroughly studied by electrochemistry in comparison to its precursor [28]. The data obtained regarding their reduction mechanisms, positive reactivity with oxygen, and analysis of the electrogenerated intermediates were useful in explaining their biological outcomes. The main results and assignments of the reduction peaks are shown in Figure 3, together with the cyclic voltammetry [52].

Nitroaromatic-acrylates, Morita-Baylis–Hillman adducts (MBHA)

Several synthetic compounds (MBHA, Figure 1b) with significant leishmanicidal activity were investigated by electrochemical methods (CV, DPV) and computational studies. A strong correlation was obtained between Epc1 (first wave reduction potential) and IC50 values. Softer compounds (lower molecular hardness, N) was the most bioactive against Leishmania amazonensis [53,54]. The main results and assignments of the reduction peaks are shown in Figure 3, together with the cyclic voltammetry of the ortho-derivative.

These are just some examples of the potential use of electrochemistry in the area of nitro-containing drugs.

Conclusions and perspectives

Electrochemistry has been used to further validate proposed biological reduction mechanisms of compounds that are eligible for preliminary and complementary biological screening. Electrochemical techniques were used to choose the best leads against etiologic agents of several diseases. Computational estimation of redox potentials (typically versus NHE and in aprotic medium) helped design the best prototypes. However, the performing of complete electrochemical experiments (CV, DPV, SWV, electrolysis, and others) would be much more influential, including pieces of evidence of the electrogenerated products, positively mimicking *in vitro* and *in vivo* metabolism. When coupled with other techniques (*in situ*, spectroelectrochemistry) would allow a much more precise and in-depth view of the process. The electrochemical methods do well to predict the molecular mechanism of the present class of compounds. As an additional competitive advantage, electrochemistry allows verifying reductive cleavage *in situ*, the generated intermediates' characterization, and the measure of the number of transferred electrons. By controlling the bioactivation of nitro compounds toward the maximization of such compounds' bioactive potential, with a concomitant minimization of toxicity issues, would lead to these prodrugs' therapeutic growth. As such, it is recommended to continue to explore the redox mechanisms through theoretical and experimental approaches.

Electrochemistry, in drug discovery and development, has several desirable features and can be a useful guide to the understanding of the phenomena of electron transfer and further applications.

Authors' contributions

Jadriane de Almeida Xavier: Formal analysis, Visualization, Writing. Thaissa L. Silva: Formal analysis, Visualization, Writing. Eduardo Caio Torres-Santos: Writing – review & editing. Camila Calado de Vasconcelos: Methodology, investigation. Anastacio Boane: Methodology, investigation. Ricardo Alexandre dos Santos: Methodology, investigation. Andre Felippe A. Xavier: Methodology, investigation. Marília O. F. Goulart: Conceptualization, Writing – review & editing, Funding acquisition, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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